American Journal of Medical Genetics 68:1–6 (1997)

Association of Late Onset Spastic Paraparesis and Dementia: Probably an Autosomal Dominant Form of Complicated Paraplegia

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The hereditary paraplegias are a heterogeneous group of genetic disorders characterized mainly by spastic paraparesis, which may be found as an isolated "pure form" known as Strümpell-Lorrain syndrome, or associated with a wide group of other manifestations [Harding, 1990; McKusick, 1994]. We studied two unrelated families, one with five members and the other with 11 members (over four generations), affected by a syndrome of late onset spastic paraparesis and dementia. Both pedigrees suggest an autosomal dominant pattern of inheritance. However, this cannot be concluded definitely because male-to-male transmission was not seen. Since this disorder has a late age of onset, we still do not know who will become affected in the second, third, and fourth generations. The association of late onset spastic paraparesis and dementia, without other pathological findings, has not been reported and probably represents a distinct entity. Am. J. Med. Genet. 68:1–6, 1997 © 1997 Wiley-Liss, Inc.

KEY WORDS: autosomal dominant; complicated paraplegia; dementia; hereditary; spastic paraparesis

INTRODUCTION

Associations of spastic paraparesis and a variable combination of other manifestations, such as dementia, retinal degeneration, optic atrophy, retinitis pigmentosa, glaucoma, precocious puberty, skin/hair pigmentation abnormalities, microcephaly, brachydactyly, and mild facial anomalies, have been described previously and named "complicated paraplegias." We have observed an association of late-onset spastic paraparesis and dementia without other anomalies, in 16 members of two unrelated families. We suggest, based on the analysis of the pedigrees and a review of the literature, that this form of complex paraplegia probably is a distinct autosomal dominant entity.

FAMILY DATA

Family 1

The propositus (Fig. 1, II-3) and one of his brothers (II-4) developed a syndrome of abnormal gait at the ages of 47 and 45 years, respectively. Later, a progressive form of dementia appeared, characterized by memory loss, emotional changes, judgment disturbances,

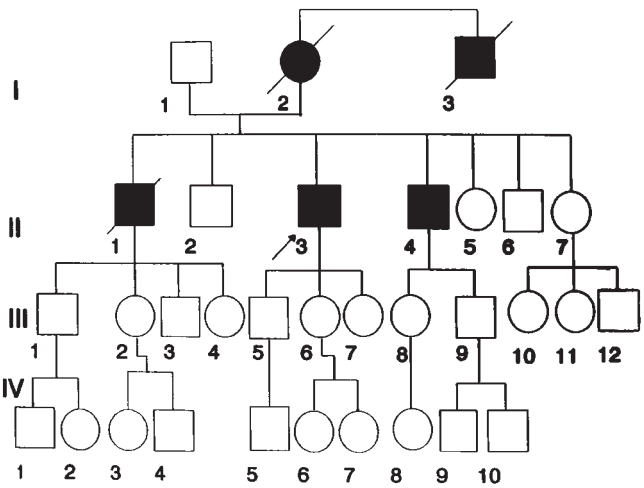

Fig. 1. Pedigree of family 1.

Contract grant sponsor: COLCIECIAS

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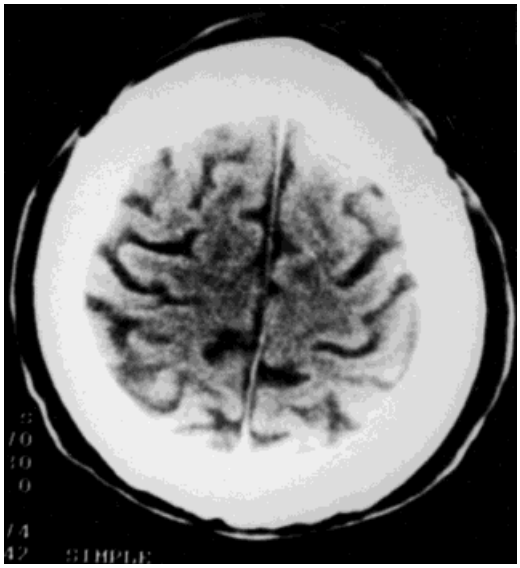
Received 10 January 1995; Accepted 2 January 1996

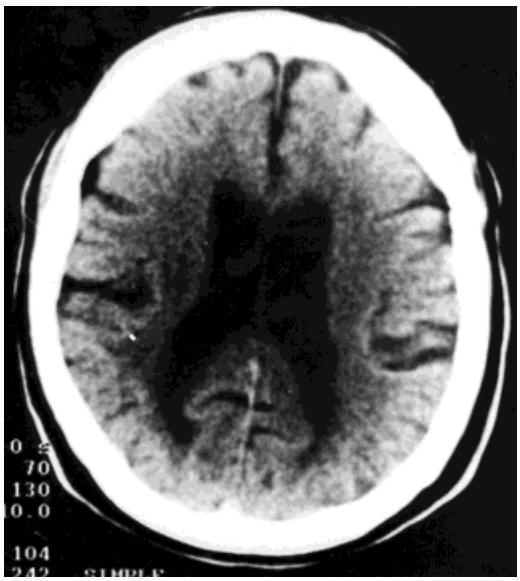
TABLE I. Differential Diagnosis of the Hereditary Complicated Paraplegias*

Entity	Distinctive features	PK	References
Strumpell disease MIM: *182600, *270800, *312900	Pure hereditary spastic paraparesis	AD AR XL	Boustany et al. [1987], Cooley et al. [1990], Rothschild et al. [1979], Goldblatt et al. [1989]
Spastic paraplegia, deafness, and nephropathy MIM: 182690	Bilateral sensorineural deafness Intellectual impairment Nephropathy	Probably AD	Fitzsimmons et al. [1988]
Silver disease MIM: 182700	Onset in the second decade Slight progression Normal life span Amyotrophy of the hands	Probably AD	McKusick [1994]
Spastic paraplegia with extrapyramidalism MIM: 182800	Clinical manifestations of extrapyramidalism	Probably AD	McKusick [1994]
Spastic paraplegia, optic atrophy, and dementia MIM: 182830	Early age of onset, first manifestations may appear as early as the first decade	Probably AD	Rothner and Yahr [1976], Katz et al. [1992]
Spastic paraplegia and branchial myoclonus	Rhythmic myoclonus of palate, pharynx, larynx, and face Truncal ataxia	Probably AD	de Yebenes et al. [1988]
Ataxia of Charlevoix-Saguenay MIM: *270550	Early onset Ataxia, dysarthria, nystagmus, mitral valve prolapse, muscular atrophy	AR	McKusick [1994]
Infantile spastic diplegia MIM: *207600	Mental deficiency	AR	Gustavson et al. [1989]
Lison syndrome MIM: 270680	Skin manifestations: vitiligo, hyperpigmentation of exposed areas, multiple lentigines, premature graying of hair, café-au-lait spots	Probably AR	Lison et al. [1981]
Spastic paraplegia and retinal degeneration MIM: *270700	Macular degeneration Mild mental retardation	AR	McKusick [1994]
Spastic paraplegia, and pigmentary abnormalities MIM: 270750	Early onset of paraparesis (first decade) Peripheral neuropathy Depigmented areas of skin and hair	Probably AR	Stewart et al. [1981]
Spastic paraplegia, and glaucoma MIM: 270850	Glaucoma Mental retardation	Probably AR	Chenevix-Trench et al. [1986]
Spastic quadriplegia, and retinitis pigmentosa MIM: 270950	Retinitis pigmentosa Mental retardation	Probably AR	McKusick [1994]
Troyer syndrome MIM: *275900	Early onset Delayed development Distal muscle wasting Dysarthria Choreoatetosis Pseudobulbar palsy	AR	Neuhauser et al. [1976]
Sjogren-Larsson syndrome MIM: *270200	Short stature Seizures Retinal degeneration Ichtyosiform skin changes	AR	Jagell et al. [1981], Jagell and Linden [1982]
MAST syndrome MIM: *248900	Early onset (second–third decade) Basal ganglion manifestations such as dysarthria, and athetosis	AR	McKusick [1994]

Spastic paraplegia, and hereditary sensory neuropathy MIM: 256840	Early onset (as early as first decade) Painless perforating and mutilating ulcers of the hands and feet Loss of pain and of the sensations of touch, heat, and cold over the feet Shooting pains in the legs, and occasionally in arms	Probably AR	McKusick [1994]
Spastic paraplegia and brachydactyly type E MIM: 270710	Skeletal anomalies of the hands and feet: brachydactyly, cone shaped epiphyses Dysarthria	Uncertain	Fitzsimmons and Guilbert [1987]
Spastic paraplegia and optic nerve hypoplasia	Bilateral hypoplasia of the optic nerve Pupillary tight-near dissociation Peripheral neuropathy Fasciculations Cardiomyopathy	Uncertain	Doro et al. [1988]
X-linked complicated spastic paraplegia MIM: *312900	Heterogeneous group of conditions Spastic paraparesis can be associated with a wide group of abnormalities,such as: nystagmus, cerebellar signs, optic nerves involvement, mental retardation, muscular abnormalities	XL	Gutmann et al. [1990], Leppert et al. [1987], McKusick [1992], Zatz et al. [1976]
Spastic paraparesis and deafness MIM: 312910	Onset in the first decade Short stature Hypogonadism Lens opacities Deafness	Probably XL	Wells and Jankovic [1986]
MASA syndrome MIM: *303350	Mental retardation Aphasia Adducted thumbs Lumbar hyperlordosis	XL	Bianchine and Lewis [1974], Straussberg et al. [1991], Yeatman [1984]
Kjellin syndrome	Dysarthria Ataxia Mental retardation Pigmentary macular degeneration	Probably AR	Farmer [1985]

* MIM: McKusick's catalogue number; PH: pattern of inheritance; AD: autosomal dominant; AR: autosomal recessive; XL: X-linked.





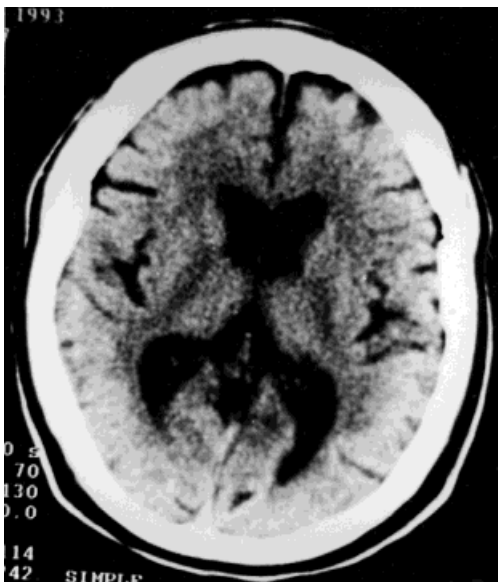


Fig. 2. Brain CT-SCAN findings.

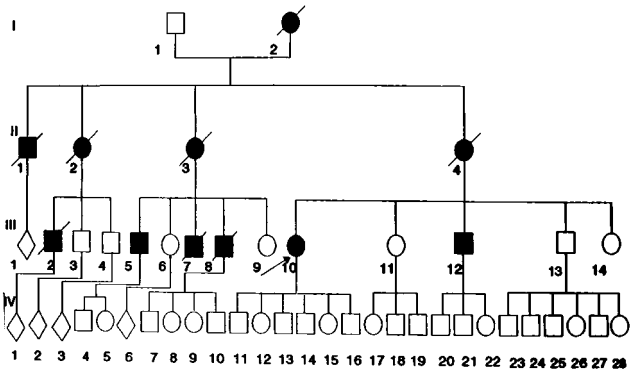


Fig. 3. Pedigree of family 2.

and language alterations. These clinical manifestations progressed from hypokinesia to akinesia, leading the patients to social isolation and limiting them to rest in bed.

Physical examination of II-3 and II-4 demonstrated, in both, spastic paraparesis with marked alteration of gait and pyramidal signs in the lower limbs. Spasticity was moderate in II-3 and severe in II-4. Muscular size and strength were normal, and abnormal movements were not observed. Cranial nerves were unaffected, tendon reflexes in the upper limbs were normal, and vibration sense was not evaluable. Psychological tests confirmed dementia. The ophthalmological evaluation and the electrophysiological examination, including electromyography (EMG), and nerve conduction velocity (NCV) studies were normal. GTG-banded karyotypes showed normal chromosomes, and CT-scan showed diffuse cortical and subcortical atrophy (Fig. 2).

The propositus' oldest brother, his mother, and his uncle (II-1, I-2, and I-3 in Fig. 1, respectively), were considered affected, because their clinical records, and relatives' descriptions were concordant with the clinical picture found in those individuals previously reported.

Family 2

A late onset form of spastic paraparesis preceding progressive dementia, were the main findings of the clinical picture observed in the 46-year-old proposita, in one of her brothers, and in one of her cousins. The ages of onset were 43, 40, and 44 years. (Fig. 3: III-10, III-12, and III-5, respectively).

Their neurological findings were like those presented by the members of family 1. Nevertheless, in III-5, bilateral optic atrophy was demonstrated by the ophthalmological evaluation, but we cannot determine its time of apparition. In III-10, mild amiotrophy of the hands was observed. The spasticity of the lower limbs was moderate in the three patients.

The psychological evaluation showed indifference, disminution of corporal expression, hypoprosexia, allopsychic disorientation, affective instability, poor

judgment, and memory disturbances. The GTG-banded chromosomes and the electrophysiological studies (EMG, and NVC) were normal. The brain CT-scan findings were as those found in the members of family 1.

Eight relatives of the proposita (Fig 3: I-2, II-1, II-2, II-3, II-4, III-2, III-7, III-8) died before we met this family, and their medical records were not available. Nevertheless, we considered them affected because the clinical pictures referred by other relatives matched exactly those previously described.

DISCUSSION

We have studied two unrelated families affected by a hereditary syndrome characterized mainly by spastic paraparesis and dementia, clinical manifestations that led them to a state of complete dependency, and social isolation. Intercurrent respiratory infection while bedridden was the principal cause of death.

The sex ratio was 10 M: 6 F, and the average age of onset was 44.9 years (range: 40–48). The life expectancy of the affected relatives was reduced to 53.2 years (range: 45–60). Both pedigrees are consistent with a dominant pattern of inheritance. However, there are two facts that did not allow us to establish if this entity is inherited in an autosomal or an X-linked pattern: (1) male-to-male transmission was not present, and (2) a great number of relatives have not reached the fifth decade of life, when the first manifestations of the syndrome typically appear. We cannot predict who will develop the syndrome in the future.

An insidious stiffness in the legs, which gradually progresses to spastic weakness, with increasing difficulty in walking, was the initial symptom in our patients. All the affected became bedridden after a period of 5.5 (± 1) years.

The first manifestations of dementia appeared 2 years after the initial neurological symptoms. They progressed from short-term memory loss to complete dementia over a period of 2–4 years. During the third year, the patients developed insomnia, lacunar amnesia, and interpersonal relations were affected. Finally, allopsychic disorientation was evident and the patients showed confusion and emotional instability.

Differential diagnosis included all the syndromes of hereditary paraplegia presented in Table I. All could be excluded based on the lack of associated manifestations other than late onset dementia. Nevertheless, we want to point to reports by Rothner and Yahr [1976] and by Katz et al. [1984]. The affected individuals in those studies (same family) have a clinical picture that differs from that of our families. Early optic atrophy, an abnormality documented in only one of our patients, was present in all their cases. Also, the age of onset in their family occurred as early as the first decade, and the only adult described (the mother of five affected children) presented dementia, spastic paraparesis, and optic atrophy during the fourth decade.

Although the two families described here may be affected by the same condition, it is possible that they have two entities with different etiologies, but with a very similar phenotype. Alternately, we suggest the possibility of allelic heterogeneity between the disorder affecting our two families and the one described by Rothner and Yahr [1976].

Some forms of familial spastic paraparesis have now been mapped by means of linkage analysis, and genetic heterogeneity has been demonstrated. Some of the loci identified are located on 2p, 14q, 15q, and Xq. [Dubé et al., 1995; Fink et al., 1995; Fransen et al., 1995; Gispert et al., 1995; Hazan et al., 1993; Kenwrick et al., 1986; Lennon et al., 1995; Nance et al., 1995; Zatz et al., 1995]. The form of complicated paraplegia described in our families could belong to one of these mapped entities or could represent a new and separate entity. This will be resolved by testing the above markers in the described pedigrees.

ACKNOWLEDGMENTS

The authors are grateful to Peter Stucky for the language revision, and to Armando Alcaraz and Jorge Jején for the artwork.

REFERENCES

Bianchine JW, Lewis RC Jr (1974): The MASA syndrome: A new heritable mental retardation syndrome. Clin Genet 5:298–306.

Boustany RMN, Fleischnick E, Alper CA, Marazita ML, Spence MA, Martin JB, Kolodny EH (1987): The autosomal dominant form of "pure" familial spastic paraplegia: Clinical findings and linkage analysis of a large pedigree. Neurology 37:910–915.

Chenevix-Trench G, Leshner R, Mamunes P (1986): Spastic paresis, glaucoma and mental retardation. A probable autosomal recessive syndrome? Clin Genet 30:416–421.

Cooley WC, Rawnsley E, Melkonian G, Moses C, McCann D, Virgin B, Coughlan J, Moeschler JB (1990): Autosomal dominant familial spastic paraplegia: Report of a large New England family. Clin Genet 38:57–68.

de Yebenes JG, Vazquez A, Rabano J, de Seijas EV, Urra DG, Obregon MC, Barquero MS, Arribas MA, Moreno JL, Alenda JR (1988): Hereditary branchial myoclonus with spastic paraparesis and cerebellar ataxia: A new autosomal dominant disorder. Neurology 38:569–572.

Doro D, Rossetti A, Battistella PA, Fardin P, Moro F (1988): Optic nerve hypoplasia associated with pupillary light-near dissociation, spastic paraparesis, and other non-ocular anomalies. Ital J Neurol Sci 9:509–513.

Dubé MP, Rouleau GA, Kibar Z, Farlow MR, Ebers G, Harper P, Kolodny EH, Baumbach L, Figlewicz DA (1995): Autosomal dominant hereditary spastic paraplegia: Linkage analysis of a heterogeneous trait (abs). Am J Hum Genet 57(suppl):A190.

Farmer SG, Longstreth WT Jr, Kalina RE, Todorov ABSO (1985): Fleck retina in Kjellin's syndrome. Am J Ophthalmol 99:45–50.

Fink JK, Wu CB, Jones SM, Sharp GB, Lange BM, Lesicki A, Reinglass T, Varvil T, Otterud B, Leppert M (1995): Autosomal dominant familial spastic paraplegia: Tight linkage to chromosome 15q. Am J Hum Genet 56:188–192.

Fitzsimmons JS, Guilbert PR (1987): Spastic paraplegia associated with brachydactyly and cone shaped epiphyses. J Med Genet 24: 702–705.

Fitzsimmons JS, Watson AR, Mellor D, Guilbert PR (1988): Familial spastic paraplegia, bilateral sensorineural deafness, and intellectual retardation associated with a progressive nephropathy. J Med Genet 25:168–172.

Fransen E, Van Camp G, Vits L, Coucke P, Willems PI (1995): CRASH syndrome: The clinical spectrum of mutations in L1 including Corpus callosum agenesis, retardation, adducted thumbs, spastic paraplegia and hydrocefalus (abs). Am J Hum Genet 57(suppl): A212.

Gispert S, Santos N, Damen R, Voit T, Schulz J, Klockgether T, Orozco G, Kreuz F, Weissenbach J, Auburger G (1995): Autosomal dominant familial spastic paraplegia: Reduction of the FSPI candidate region on chromosome 14q to 7 cM and locus heterogeneity. Am J Hum Genet 56:183–187.

Goldblatt J, Ballo R, Sachs B, Moosa A (1989): X-linked spastic paraplegia: Evidence for homogeneity with a variable phenotype. Clin Genet 35:116–120.

Gustavson K, Modrzewska K, Erikson A (1989): Hereditary spastic diplegia with mental retardation in two young siblings. Clin Genet 36:439–441.

Gutmann DH, Fischbeck KH, Kamholz J (1990): Complicated hereditary spastic paraparesis with cerebral white matter lesions. Am J Med Genet 36:251–257.

Harding AE (1990): The hereditary ataxias and paraplegias. In Emery AEH, Rimoin DL (eds): "Principles and Practice of Medical Genetics." London: Churchill Livingstone, pp 383–396.

Hazan J, Lamy C, Melki J, Munnich A, de Recondo J, Weissenbach J (1993): Autosomal dominant familial spastic paraplegia is genetically heterogeneous and one locus maps to chromosome 14Q. Nature Genet 5:163–167.

Jagell S, Gustavson KH, Holmgren G (1981): Sjogren-Larsson syndrome in Sweden: a clinical, genetic and epidemiological study. Clin Genet 19:233–256.

Jagell S, Linden S (1982): Ichtyosis in the Sjogren-Larsson syndrome. Clin Genet 21:243–252.

Katz DA, Nassem A, Horoupian DS, Rothner AD, Davies P (1984): Familial multisystem atrophy with possible thalamic dementia. Neurology 34:1213–1217.

Kenwrick S, Ionasescu V, Ionasescu G, Serbay Ch, King A, Dubowitz M, Davies KE (1986): Linkage studies of X-linked recessive spastic paraplegia using DNA probes. Hum Genet 73:264–266.

Lennon F, Gaskell PC, Wolpert C, Aylsworth AS, Malin D, Warner C, Farrel CD, Boustany RN, Albright SG, Kingston HM, Cummings WJK, Hogan EL, Vance JM, Pericak-Vance MA (1995): Linkage and heterogeneity in hereditary spastic paraparesis (abs). Am J Hum Genet 57(suppl):A217.

Leppert M, Keppen L, O'Connell P, Nakamura Y, Stauffer D, Lathorp M, Lalouel J, White R (1987): Etiological heterogeneity in X-linked spastic paraplegia (abs). Cytogenet Cell Genet 46:648.

Lison M, Kornbrut B, Feinstein A, Hiss Y, Boichis H, Goodman RM (1981): Progressive spastic paraparesis, vitiligo, premature graying, and distinct facial appearance: A new genetic syndrome in 3 sibs. Am J Med Genet 9:351–357.

McKusick VA (1994): Mendelian Inheritance in Man. In: "Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes," Baltimore: Johns Hopkins University Press, 11th ed.

Nance MA, Raabe WA, Midani H, David WS, Megna L, Pericak-Vance MA, Haines JL (1995): Confirmation of linkage of familial spastic paraparesis to chromosome 2p21(abs). Am J Hum Genet 57(suppl):A222.

Neuhauser G, Wiffler C, Opitz JM (1976): Familial spastic paraplegia with distal muscle wasting in the Old Order Amish: Atypical Troyer syndrome or "new" syndrome. Clin Genet 9:315–323.

Rothner AD, Yahr MD (1976): Familial spastic paraparesis, optic atrophy, and dementia. NY State J Med 76:756–758.

Rothschild H, Happel L, Rampp D, Hackett E (1979): Autosomal recessive spastic paraplegia: Evidence for demyelination. Clin Genet 15:356–360.

Stewart RM, Tunell G, Ehle A (1981): Familial spastic paraplegia, peroneal neuropathy, and crural hypopigmentation: A new neurocutaneous syndrome. Neurology 31:754–757.

Straussberg R, Blatt I, Brand N, Kessler D, Katznelson MBM, Goodman RM (1991): X-linked mental retardation with bilateral clasped thumbs: Report of another affected family. Clin Genet 40: 337–341.

Wells CR, Jankovic J (1986): Familial spastic paraparesis and deafness: A new X-linked neurodegenerative disorder. Arch Neurol 43: 943–946.

Yeatman GW (1984): Mental retardation-clasped thumb syndrome. Am J Med Genet 17:339–344.

Zatz M, Penha-Serrano C, Otto PA (1976): X-linked recessive type of pure spastic paraplegia in a large pedigree: absence of detectable linkage with Xg. J Med Genet 13:217–222.

Zatz M, Marie SK, Passos-Bueno MR, Ungar D (1995): An autosomal form of dominant spastic paraplegia affecting almost exclusively males (abs). Am J Hum Genet 57(suppl):A106.